

wherein [the size distribution of] a group of [micellar complexes comprising] said micellar [complexes has a] complexes have a substantially homogeneous size distribution.

27. (Amended) A group of micellar complexes comprising a micellar complex according to claim 25, wherein the size distribution of [a] the group of micellar complexes varies [by] less than 20% [relative to the average size of a complex in said group of micellar complexes].

REMARKS

Applicants respectfully request reconsideration of the rejections in view of the following remarks. With the entry of this Amendment, claims 1-30 of this application are currently pending. Claims 1, 4, 5, 15, 16, 20, 25, and 27 have been amended. The claims were amended in order to more clearly define the subject matter of the invention, and not to overcome prior art. No new matter has been added by these amendments.

Claim Objections

The Examiner has objected to claim 16 under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of the previous claim. Specifically, the Examiner argues that claim 16, which is drawn to a micellar complex according to claim 9, provides further limitations regarding the characteristics of a group of micellar complexes but groups of micelles are not claimed. The Examiner contends that no further limitations on individual complexes is set forth and therefore, the claimed complexes are indistinguishable from those of claim 9.

LAW OFFICES

FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Although Applicants disagree with the Examiner's interpretation of claim 16, Applicants, solely to expedite prosecution of this application, have amended claim 16 to claim a group of micellar complexes. Accordingly, Applicants respectfully request the Examiner to withdrawn the objection.

35 U.S.C. § 112, ¶ 1

The Examiner has rejected claims 1-30 under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

Specifically, the Examiner contends that the Applicants have not disclosed the production of a group of micellar complexes, which vary in size by less than 20% from the average size of the group.

Furthermore, with respect to claims 6, 13, and 21, the Examiner contends that the invention comprises the coating of micellar complexes with a "hydrophobic species." The Examiner contends that the specification provides no disclosure or examples of how one would successfully coat a micellar complex and avoid simple integration of the hydrophobic species into the micelle. In addition, the Examiner believes that coating the micellar complex is indistinguishable from the method of producing such a complex because any disassociated lipid not bound to DNA would be available to coat the cationic lipid/DNA complex. Thus, according to the Examiner, one would have to perform undue experimentation in order to develop a coating technique.

LAW OFFICES

FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Applicants respectfully traverse. Applicants define substantially homogenous size distribution on page 11 of the specification. Specifically, Applicants state that "micellar complexes of the present invention have a narrower size distribution curve than lipid complexes prepared by traditional means." See Specification, p. 11, lines 16-17. In addition, Applicants have disclosed a method of making micellar complexes wherein the size distribution of those micellar complexes is substantially homogenous. Although the Applicants method may produce micellar complexes of varying sizes, a substantial portion of those micellar complexes will fall within a homogenous size distribution. This is clearly demonstrated in Figures 2C and 3C, which shows that the micellar complexes made by Applicants' disclosed method fall with a narrow size distribution curve. The size distribution obtained by the claimed method is substantially more homogenous than the size distribution of micellar complexes formed by traditional means, which is demonstrated in Figures 2A and 2B.

Furthermore, the Examiner appears to be looking at the range, in size, of micellar complexes made by the present invention rather than the size distribution. The micellar complexes made by the claimed method will "range" in size from small to large. However, as demonstrated in Figures 2C and 3C, the size "distribution" of those micellar complexes will be substantially homogenous, *i.e.*, the majority of micellar complexes fall within a narrow area under the curve (are close in size).

Moreover, the Examiner has provided no proof to doubt that Applicants' method will not produce micellar complexes with a substantially homogenous size distribution that varies by less than 20%, especially in view of Figures 2C and 3C. Once again it is the size distribution that is

important not the size range. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection.

With respect to claims 6, 13, and 21, coating of the lipid/DNA complex with a hydrophobic species is well known in the art and, therefore, Applicants need not provide a specific example. In fact, a specification need not describe, and best omits, that which is well known in the art. See In re Buchner, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991). Furthermore, representative examples are not required by the statute and are not an end in themselves. See In re Robins, 429 F.2d 452, 457, 166 U.S.P.Q. 552, 555 (C.C.P.A. 1970).

Moreover, the coating of the micellar complexes with a hydrophobic species *is distinguishable* from the method of producing the micellar complex. A micellar complex is made by combining at least one cationic amphiphile with a PEG derivative to form a lipid micellar, which is then combined with at least one biologically active molecule, such as DNA. The micellar complex is then coated, in a separate step.

Cationic amphiphiles interact through ionic charge. Thus, the micellar complex is formed once the cationic amphiphile/PEG derivative is interacted with the biologically active molecule. One of skill in the art would know how much cationic amphiphile to use, based on the amount of biologically active molecules present. Therefore, the amount of cationic amphiphiles remaining to coat the micellar complex would be statistically insignificant.

Finally, the hydrophobic species would not be integrated into the micellar complex because, as stated above, the cationic amphiphile interacts with the biologically active molecule through an ionic charge. The hydrophobic species interacts through encapsulation and, therefore,

would not interrupt or integrate into the micellar complex. It would simply "coat" the complex, as claimed.

35 U.S.C. § 112, ¶ 2

The Examiner has rejected claims 1-16 and 25-30 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

With regard to claims 1-16 the Examiner argues that the claims are indefinite for several reasons. First, the meaning of "substantially homogenous micellar lipid" is unclear because the specification does not distinguish between substantial and insubstantial homogeneity. Second, the Examiner contends that it is unclear as what is intended to be homogenous about the lipids. Third, the Examiner contends that the term "micellar lipids" is confusing because combining a cationic lipid with a PEG derivative may result in a lipid micellar, it is unclear that this procedure would create a lipid of any kind. Fourth, the Examiner argues that the term "sufficient amount of PEG" is indefinite because it is unclear as to what constitutes a "sufficient amount." Fifth, the Examiner contends that the phrase "amount suitable" is indefinite because it is unclear as to whether the phrase applies to the cationic amphiphile, the PEG derivative, or both.

Applicants will address each of the Examiner's arguments in order.

First, the phrase "substantially homogenous micellar lipid" is defined within the specification on page 11, lines 16-17, "micellar complexes of the present invention have a narrower size distribution curve than lipid complexes prepared by traditional means." Thus, "insubstantial homogeneity" would mean that there is a broad size distribution similar to the lipid

LAW OFFICES

FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

complexes prepared by traditional means. This definition is graphically demonstrated in Figures 2C and 3C, the size distribution of the micellar complexes is substantially narrower than the size distribution of complexes prepared by traditional means, as demonstrated in Figures 2A and 2B. Therefore, the meaning of "substantially homogenous micellar lipids" is clear.

Second, with Applicant's amendment of claim 1, it is now clear that "substantially homogenous" refers to the size distribution of the micellar complexes. Accordingly, this rejection should be withdrawn.

Third, Applicants contend that the term "micellar lipid" is not confusing and the meaning is clear, as defined and used in the specification.

Fourth, the phrase "sufficient amount of PEG" is supported in the specification. A sufficient amount of PEG is an amount needed to form a micellar lipid based on the amount of cationic amphiphile being used. Determining what constitutes a sufficient amount of PEG is demonstrated and disclosed in the specification. See Specification, p. 18, line 18- p. 19, line 6; p. 38, line 15 to p. 40, line 6.

Fifth, Applicants have amended claim 1 to remove the language "in an amount suitable to produce."

For the reasons and amendments stated above, Applicants respectfully request the withdrawal of the rejection of claims 1-16.

The Examiner has also rejected claim 4 under 35 U.S.C. § 112, second paragraph because it depends from itself and claims 4 and 15 because they recite a ratio of lipids to DNA without recitation of units to measure each substance. Applicants have amended claim 4 to depend from

claim 1 and amended claims 4 and 15 to define as (vol:vol) the units for the 1:8 ratio. Therefore, the rejection of these claims should be withdrawn.

The Examiner has also rejected claims 16 and 25-30 because in those claims a single claimed complex is described in terms of the size distribution of a group of complexes. The Examiner argues that a characteristic of a group of complexes cannot be used to describe a single complex.

Applicants have amended claims 16, 25, and 27 to claim a group of micellar complexes. Thus, this amendment more clearly defines the scope of the invention. Accordingly, the rejection of these claims should be withdrawn.

Finally, the Examiner has rejected claims 25-30 because the meaning of the phrase "substantially homogenous size distribution" cannot be determined from the specification.

Applicants respectfully traverse. As discussed above, Figures 2C and 3C clearly demonstrate that the size distribution of the micellar complexes of the present invention are of a substantially homogenous size as compared to the traditional complexes disclosed in Figures 2A and 3A. Furthermore, on page 11 of the specification, the Applicants clearly state that the micellar complexes "have a narrower size distribution curve than lipid complexes prepared by traditional means." Therefore, the meaning of "substantially homogenous size distribution" can be, and is, determined from the specification. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection.

LAW OFFICES

FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

35 U.S.C. § 102

The Examiner has rejected claims 1-3, 6, 9-11, 13, 14, 16-19, 21, 22, and 24-29 under 35 U.S.C. § 102(b) as being anticipated by Harris, U.S. Patent No. 5,719,131. According to the Examiner, Harris teaches a method of making micellar complexes comprising a cationic lipid, a PEG derivatized colipid, and DNA. The Examiner indicated that claims 6, 13, and 21 were included in this rejection because the methods and compositions do not appear to be distinguishable from the teachings of Harris because it appears that coating the micellar complexes with a hydrophobic species is inherent in the method of making the initial micellar compositions. The Examiner also noted that the claims were not considered to encompass a population of micelles in which the size distribution varies by less than 20% relative to the mean size of the complexes in the group, because this limitation was not explicitly recited in the claim.

Applicants respectfully traverse. In order to anticipate a claim, a single source must contain all of the elements of the claim. See Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986). Harris does not teach each and every element of the present claims and, therefore, does not anticipate the claims of the present invention.

The Examiner states that he did not consider the claims to encompass a population of micelles in which the size distribution varies by less than 20% relative to the mean size of the complexes in a group. The Examiner should, however, consider the claims to encompass lipid micelles, which have a substantially homogenous size distribution, because this limitation is

explicitly recited in claim 1. Furthermore, the Examiner should consider claims 5, 16, and 27 to have a size distribution of less than 20%.

Harris does not teach or even suggest a method of making micellar complexes with a *substantially homogenous size distribution*. As Applicants discussed above, "substantially homogenous size distribution" is supported by the specification. Since Harris does not teach "substantially homogenous size distribution," it does not contain all of the elements of the pending claims. Accordingly, Harris does not anticipate the present invention and the rejection should be withdrawn.

The Examiner has also rejected claims 1-3, 6-14, 16-19, and 21-30 under 35 U.S.C. § 102(e) as being anticipated by Unger, U.S. Patent No. 6,028,066 filed July 2, 1997 and issued February 22, 2000. The Examiner argues that Unger teaches a method of making micellar complexes by combining micellar lipids with a bioactive agent, which may be DNA, and that the micellar lipids may contain PEG-modified lipids. According to the Examiner, the complexes of Unger may comprise targeting moieties and may include peptides with RGD sequences. Finally, Unger apparently teaches the delivery of the complexes to mammalian airway cells.

Applicants respectfully traverse. Similar to Harris, Unger does not teach each and every limitation of the claims. Specifically, Unger does not teach a method of making micellar complexes with a substantially homogenous size distribution as recited in claim 1. Because Unger does not contain all of the elements of the pending claims, it does not anticipate the present invention.

35 U.S.C. § 103

The Examiner has rejected claims 1, 4, 15, and 20 under 35 U.S.C. § 103(a) as being unpatentable over Harris, the '131 patent. According to the Examiner, Harris teaches a method of making micellar complexes wherein the cationic lipid and DNA are present in 64 different ratios including 0.7:1, 1.4:1, 5.6:1, and 11.2:1. Harris does not teach a lipid to DNA ratio of 8:1.

However, the Examiner argues that it would have been obvious to one of ordinary skill in the art to combine a cationic lipid and DNA in a ratio of 8:1. In the Examiner's view, one would be motivated to combine the components in the claimed ratio because the combination of these two components is a result-effective variable, i.e., the results of a technique using the compositions are effected by the concentrations of each component and one of ordinary skill in the art would be motivated to optimize the concentrations of each variable. Furthermore, the Examiner contends that the claimed ratio is not critical and, therefore, Harris renders claims 1, 4, 15, and 20 obvious.

Applicants respectfully traverse. Harris does not teach micellar complexes that have a substantially homogeneous size distribution. Since Harris, alone, does not teach or suggest every limitation of the claims, it does not render the presently claimed invention obvious. Accordingly, the PTO has not established a *prima facie* case on obviousness and, therefore, Applicants respectfully request the Examiner to withdraw the rejection.

LAW OFFICES

FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000



RECEIVED

OCT 25 2000

Attorney Docket No.: 06969.0028

Serial No.: 09/335,689

Page 13

TECH CENTER 1500/2000

CONCLUSION

In view of the foregoing remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: October 23, 2000

By: 

Sanya Sukduang
Reg. No. 46,390

LAW OFFICES

FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-406-4000